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Associations between Blood Lead Levels and Coronary Artery Stenosis Measured Using Coronary Computed Tomography Angiography

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Background: Lead exposure is a risk factor for increased blood pressure and cardiovascular disease, even when blood lead levels (BLLs) are within the normal range.

Objective: This study aimed to investigate the association between BLL and coronary artery stenosis (CAS) in asymptomatic adults using 128-slice dual-source coronary computed tomography (CT) angiography.

Methods: We analyzed medical records data from 2,193 adults (1,461 men and 732 women) who elected to complete a screening health examination, coronary CT angiography, and BLL measurement during 2011–2018 and had no history of CAS symptoms, cardiovascular disease, or occupational exposure to lead. Logistic regression models were used to estimate associations between moderate-to-severe CAS ($\geq$25% stenosis) and a 1-μg/dL increase in blood lead, with and without adjustment for age, sex, hypertension, diabetes mellitus, dyslipidemia, body mass index, regular exercise, smoking status, and alcohol drinking.

Results: BLLs ranged from 0.12 to 10.14 μg/dL, with an arithmetic mean of 2.71 ± 1.26 μg/dL. The arithmetic mean was higher for men than for women (2.98 ± 1.26 μg/dL vs. 2.18 ± 1.08 μg/dL, $p < 0.001$) and higher in the moderate-to-severe CAS group than in the no-CAS or <25% stenosis group (3.02 ± 1.44 μg/dL vs. 2.67 ± 1.23 μg/dL, $p < 0.001$). Moderate-to-severe CAS was significantly associated with BLL before and after adjustment, with an adjusted odds ratio for a 1-μg/dL increase in BLL of 1.14 (95% CI: 1.02, 1.26), $p = 0.017$.

Conclusions: BLL was positively associated with the prevalence of moderate-to-severe CAS in Korean adults who completed an elective screening examination for early cardiovascular disease, 94% of whom had a BLL of <5 μg/dL. More efforts and a strict health policy are needed to further reduce BLLs in the general population. https://doi.org/10.1289/EHP7351

Introduction

Lead is a well-known heavy metal environmental pollutant. It has no useful biological function in humans, and exposure to lead can lead to various adverse health effects in multiple organs and systems. Previous studies have reported significant associations between blood lead levels (BLLs) and all-cause and cardiovascular disease mortality (Lustberg and Silbergeld 2002; Menke et al. 2006; Schober et al. 2006). Moreover, several meta-analyses and review articles have reported evidence of an association between BLL and elevated blood pressure (Hertz-Picciotto and Croft 1993; Nawrot et al. 2002; Schwartz 1995; Staessen et al. 1994, 1995). Exposure to lead has also been associated with electrocardiographic abnormalities (Cheng et al. 1998), peripheral arterial disease (Navas-Acien et al. 2004), and left ventricular hypertrophy (Schwartz 1991).

Cardiovascular disease is the leading cause of mortality, with the highest disease burden worldwide (Benjamin et al. 2018). Coronary artery stenosis (CAS) is the blockage or luminal narrowing of the arteries supplying blood and oxygen to the heart muscle. The severity of CAS is a prognostic factor for life-threatening cardiovascular disease. Coronary imaging has improved with the recent development of computed tomography (CT) techniques, such as coronary CT angiography, which involve intravenous iodinated contrast medium-enhanced electrocardiographically gated CT. Accordingly, these diagnostic techniques are now widely available, and our understanding of their potential clinical uses has markedly increased (Rubin 2013). In this study, we investigated the association between BLL and CAS in an asymptomatic population using 128-slice dual-source coronary CT angiography.

Methods

Study Participants

The study population was a subset of adults >20 years of age who completed voluntary medical examinations at the Chonnam National University (CNU) Hwasun Hospital in South Jeolla Province, South Korea, between January 2011 and December 2018 and consented to the collection and use of their personal information for research purposes, in accordance with the Personal Information Protection Act of South Korea. Medical records data were anonymized and stored in the CNU Hwasun Hospital Clinical Data Warehouse, and the study protocol was approved by the institutional review board (IRB) of CNU Hwasun Hospital (IRB number CNUHH-2020-150).

Participants (or their employers) were responsible for the costs of the health examinations, which were not prompted by any symptoms or clinical indications. Of the 11,846 consenting participants who completed a health examination, 3,417 underwent elective coronary artery CT angiography to screen for early cardiovascular disease; of these, 2,316 also elected to have blood lead measurement (Figure 1). Contraindications for the screening coronary CT scan were a history of severe adverse reactions to iodinated radiocontrast media or a glomerular filtration rate of <60 mL/min per 1.73 m^2 or a serum creatinine level of

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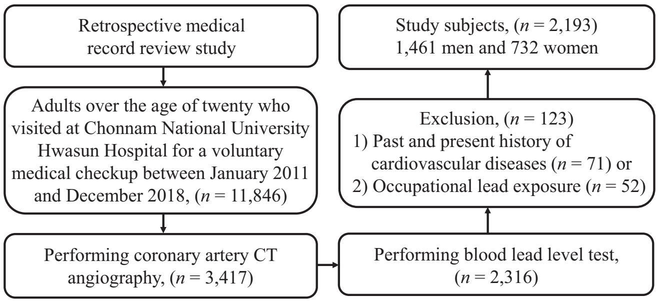

Figure 1. Information on the selection of study participants. Note: CT, computed tomography.

≥1.4 mg/dL. In addition, patients who took metformin diabetes medication on the day of the health examination had to reschedule their CT angiography for another day. Participants were excluded from the present analysis if they had a current or past history of cardiovascular disease other than essential hypertension (angina pectoris, myocardial infarction, stent insertion, cardiac arrest, arrhythmia, and other such diseases) ($n = 71$), or a history of occupational lead exposure (welding, grinding, brazing, soldering, casting, battery-related work, and other such work) ($n = 52$), leaving a total of 2,193 participants (1,461 men and 732 women).

Data Collection

All participants who completed elective health examinations during 2011–2018 were interviewed by physicians using a structured questionnaire with questions on smoking, alcohol drinking, regular exercise, history of disease, and family history of cardiovascular disease. Height and weight were measured in the upright position without shoes and socks. Blood pressure was measured in the left upper arm using a regularly calibrated electronic sphygmomanometer after the participant had been stable for >10 min. Total cholesterol, low-density lipoprotein (LDL) and high-density lipoprotein cholesterol, triglycerides, and blood glucose levels were measured in blood samples collected after 12 h of fasting.

Regular exercise was defined as performing regular physical activity for more than 30 min per day and more than once a week. Participants who had smoked less than five packs of cigarettes in their life were classified as nonsmokers, whereas those who had stopped smoking or who smoked currently were classified as ex-smokers and current smokers, respectively. Participants who ingested more than 20 g of alcohol more than once a week were classified as alcohol drinkers. Obesity was defined as a body mass index (BMI; kg/m^2) of ≥25, according to guidelines set by the South Korean Ministry of Health and Welfare (Seo et al. 2019). Participants who were taking antihypertensive medications or had a systolic blood pressure of ≥140 mmHg or a diastolic blood pressure of ≥90 mmHg at the time of the examination were classified as hypertensive. Participants who were being treated for diabetes mellitus or had fasting glucose levels ≥126 mg/dL or glycated hemoglobin (HbA1c) levels ≥6.5% at the time of the health examination were classified as having diabetes. Participants with total cholesterol levels of ≥240 mg/dL, LDL cholesterol levels of ≥160 mg/dL, or triglyceride levels of ≥500 mg/dL at the time of the health examination, were classified as having dyslipidemia.

Blood Lead Measurements

Whole blood (3 mL) was collected using a disposable syringe and placed in a K2 ethylenediaminetetraacetic acid vacuum tube. The syringe and tube were made of metal-free products. After collection, samples were mixed well and stored in a refrigerator at 4°C (2–8°C) for up to 3 d before analysis. BLLs were analyzed according to Korea Occupational Safety and Health Agency (KOSHA) guidelines (KOSHA 2017) using an atomic absorption spectrometer (Shimadzu) attached to a graphite furnace atomizer (GFA-EX7; Shimadzu). Stored samples were mixed for ≥30 min, and 0.1 mL of whole blood was diluted with 0.8 mL of 1% Triton X-100. All BLL measurements conducted during the study period (2011–2018) were performed by a single analyst under identical laboratory conditions. To verify the validity and reliability of the analysis, external quality control was performed, and laboratory conditions and the proficiency of the analyst were assessed every 2 y by KOSHA, and internal quality control was performed using standard reference material. The limit of detection (LOD) was 0.01 μg/dL. No samples had lead levels below the LOD.

Coronary Artery Stenosis

Coronary CT angiography was performed using 128-slice dual-source CT equipment (SOMATOM Definition Flash). To assess CAS, electrocardiographically gated axial images of the heart were obtained after intravascular administration of a contrast medium (Ultravist; Schering AG). The intensity of the contrast-enhanced portion of the coronary lumen at the site of maximal stenosis was measured and compared with the mean values obtained for the proximal and distal sites. After imaging, two experienced and certified cardiovascular radiology specialists evaluated the degree of narrowing of the inner diameter of the coronary artery. When there was a discrepancy in the readings recorded by the radiology specialists, the final values were decided by consensus. All analyses were performed by the same two radiology specialists during the study period. Both were qualified by the Certification Board of Cardiovascular Computed Tomography. The Korean Society of Cardiovascular Imaging recognizes this qualification, and training and evaluation are required for renewal of the certification every 5 y. In the evaluations conducted, the degree of stenosis was described as the percentage of narrowing. The degree of stenosis was classified according to the guidelines of the Coronary Artery Disease-Reporting and Data System (Ramanathan et al. 2019) as follows: *a*) no stenosis (0% narrowing); *b*) mild stenosis (>0% and <25% narrowing); *c*) moderate stenosis (≥25% and <70% narrowing); and *d*) severe stenosis (≥70% narrowing) (Figure 2). In the present study, for the purpose of statistical analyses, moderate-to-severe coronary artery narrowing (≥25% stenosis) was defined as moderate-to-severe CAS (MSCAS).

Statistical Analysis

Differences in the prevalence of CAS according to categorical variables were evaluated using the Pearson chi-square test. BLLs exhibited a right-skewed distribution (Figure 3); therefore, differences in natural log-transformed BLLs according to participant characteristics were compared using a Student's *t*-test or analysis of variance (Table S1). Logistic regression models were used to estimate odds ratios (ORs) and 95% confidence intervals (CIs) for MSCAS (≥25% stenosis) in association with a 1-μg/dL increase in BLL in the population as a whole and after stratification by sex. Models were adjusted for covariates that were significant predictors of MSCAS in bivariate models (Table S2), with increasing levels of adjustment for Model 1 [adjusted for age (continuous) and sex]; Model 2 [age, sex, BMI (continuous), regular exercise (yes/no), smoking (ever/never), and alcohol consumption (yes/no)]; and Model 3 [Model 2 covariates plus hypertension (yes/no), diabetes mellitus (yes/no), dyslipidemia (yes/no)]. Given the importance of cigarette smoking as a

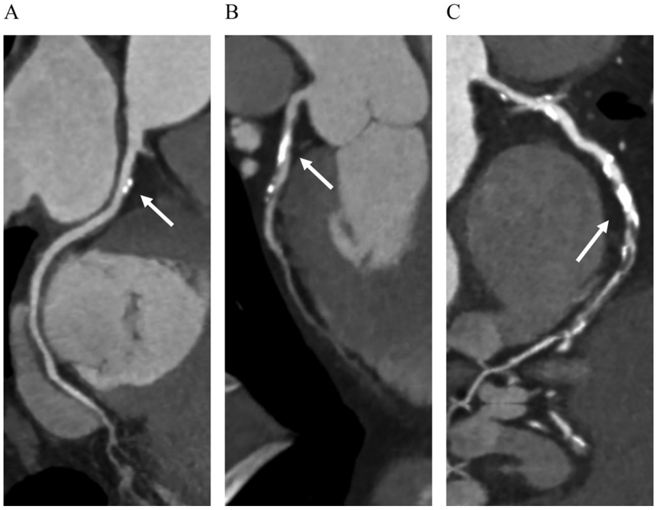

Figure 2. Coronary artery stenosis visualized using 128-slice dual-source coronary computed tomography angiography. (A) Mild stenosis in left circumflex artery, (B) moderate stenosis in left anterior descending artery, and (C) severe stenosis in right coronary artery.

potential confounder, we repeated Models 2 and 3 after replacing smoking (ever/never) with pack-years of smoking (continuous, with never smokers assigned a value of 0). All statistical analyses were performed using SPSS (version 26.0; SPSS Inc.), and the significance level was defined as $p < 0.05$.

Results

Among the 2,193 participants, there were 1,461 (67%) men and 732 (33%) women. Ages ranged from 23 to 81 y, with a mean of 53.5 ± 8.3 y (men: 52.9 ± 8.2 y, women: 54.9 ± 8.5 y). The prevalence of obesity (BMI >25) was 46% among men and 31% among women (Table 1), and the average BMI was also higher in men than women (24.8 ± 2.8 vs. 23.9 ± 2.9, respectively). Men were also more likely than women to consume alcohol (79% vs. 38%), be current or former smokers (77% vs. 3%), and be classified as having hypertension (30% vs. 27%) and diabetes mellitus (19% vs. 14%). Regular exercise was reported by 54% of men and women, and the prevalence of dyslipidemia was 23% in men and women. Of the total number of participants, 296 (14%) had

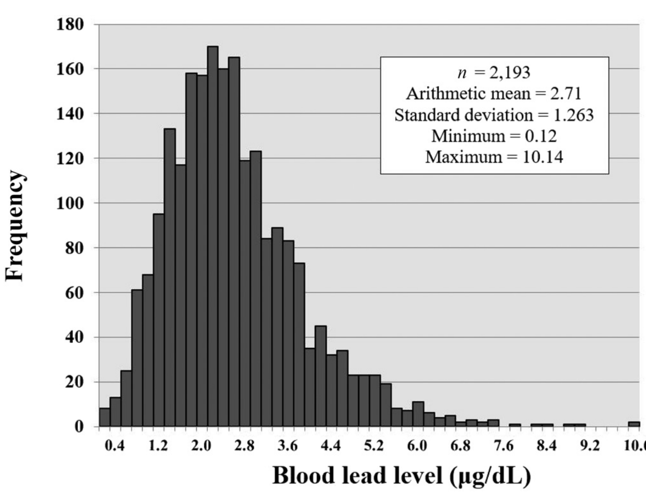

Figure 3. Blood lead level distribution of study participants.

mild CAS (>0 and <25% stenosis), and 250 (11%) had MSCAS (≥25% stenosis) (Table 1).

Overall, BLLs ranged from 0.12 to 10.14 μg/dL. The arithmetic mean was 2.71 ± 1.26 μg/dL overall and was significantly higher in men (2.98 ± 1.26 μg/dL) than women (2.18 ± 1.08 μg/dL, $p < 0.001$) (Table 2). Mean BLL was highest in the 50- to 59-y age group (2.78 ± 1.24 μg/dL) (Table S1). Other significant predictors of higher BLL were BMI, smoking, and alcohol consumption, whereas diabetes was associated with lower BLL. With respect to CAS, mean BLL was significantly higher in the group with ≥25% stenosis than in participants with 0 to <25% stenosis (3.02 ± 1.44 μg/dL vs. 2.67 ± 1.23 μg/dL).

The prevalence of MSCAS was higher in men ($n = 200$, 13.7%) than in women ($n = 50$, 6.8%). Older age, hypertension, dyslipidemia, and diabetes mellitus were significant predictors of MSCAS overall, and in men and women. Obesity, smoking, pack-years of smoking, alcohol consumption, and a lack of regular exercise were also significant predictors of MSCAS in the overall population (Table S2).

Because the general characteristics of the participants differed significantly according to sex, the association between MSCAS and BLL was analyzed after stratification by sex. In all participants, the fully adjusted (Model 3) OR for a 1-μg/dL increase in BLL was 1.14 (95% CI: 1.02, 1.26) (Table 3). Corresponding ORs for men and women were 1.14 (95% CI: 1.01, 1.28) and 1.10 (95% CI: 0.86, 1.41), respectively. Model estimates were very similar when adjusted for pack-years of smoking instead of smoking (ever/never); for example, for all participants, the Model 3 OR was 1.13 (95% CI: 1.02, 1.26) (Table S3).

Table 1. General characteristics of study participants.

	n (%)			
Variables	Total ($n = 2,193$)	Men ($n = 1,461$)	Women ($n = 732$)	*p*-Value[a]
Age (y)				<0.001
<40	80 (3.6)	54 (3.7)	26 (3.5)	
≥40 to <50	641 (29.2)	480 (32.9)	161 (22.0)	
≥50 to <60	962 (43.9)	624 (42.7)	338 (46.2)	
≥60	510 (23.3)	303 (20.7)	207 (28.3)	
BMI (kg/m^2)				<0.001
<25	1,291 (58.9)	786 (53.8)	505 (69.0)	
≥25	902 (41.1)	675 (46.2)	227 (31.0)	
Smoking				<0.001
Nonsmoker	1,053 (48.0)	344 (23.5)	709 (96.9)	
Ex-smoker	529 (24.1)	526 (36.0)	3 (0.4)	
Current smoker	611 (27.9)	591 (40.5)	20 (2.7)	
Alcohol drinking				<0.001
No	760 (34.7)	308 (21.1)	452 (61.7)	
Yes	1,433 (65.3)	1,153 (78.9)	280 (38.3)	
Regular exercise				0.823
No	999 (45.6)	668 (45.7)	331 (45.2)	
Yes	1,194 (54.4)	793 (54.3)	401 (54.8)	
Hypertension				0.104
No	1,554 (70.9)	1,019 (69.7)	535 (73.1)	
Yes	639 (29.1)	442 (30.3)	197 (26.9)	
Dyslipidemia				0.952
No	1,691 (77.1)	1,126 (77.1)	565 (77.2)	
Yes	502 (22.9)	335 (22.9)	167 (22.8)	
Diabetes mellitus				0.002
No	1,817 (82.9)	1,185 (81.1)	632 (86.3)	
Yes	376 (17.1)	276 (18.9)	100 (13.7)	
Degree of CAS				<0.001
None (0%)	1,647 (75.1)	1,039 (71.1)	608 (83.1)	
Mild (>0% and <25%)	296 (13.5)	222 (15.2)	74 (10.1)	
Moderate (≥25% and <70%)	184 (8.4)	148 (10.1)	36 (4.9)	
Severe (≥70%)	66 (3.0)	52 (3.6)	14 (1.9)	

Note: BMI, body mass index; CAS, coronary artery stenosis.
[a]Comparison by Pearson chi-square test between men and women.

Table 2. Blood lead level distribution of study participants.

Variables	n	Blood lead level (μg/dL) Arithmetic mean ± SD	Min.	25th percentile	50th percentile	75th percentile	Max.	Geometric mean (GSD)
All participants	2,193	2.71 ± 1.26	0.12	1.84	2.53	3.38	10.14	2.43 (1.64)
Men	1,461	2.98 ± 1.26	0.12	2.11	2.78	3.64	10.01	2.72 (1.56)
Women	732	2.18 ± 1.08	0.20	1.44	2.03	2.68	10.14	1.93 (1.67)

Note: GSD, geometric standard deviation; max., maximum; min., minimum; SD, standard deviation.

Discussion

Under the influence of strict policies in many countries, lead exposure in the environment has been decreasing for decades (Muntner et al. 2005). Data from the U.S. National Health and Nutrition Examination Survey (NHANES) have showed a substantial decrease in the BLLs among individuals aged 20–74 y in the United States. During 1976–1980 and 1988–1991, the geometric mean BLL decreased by 78%, from 13.1 to 3.0 μg/dL (Pirkle et al. 1994). In South Korea, according to the Korea NHANES (KNHANES) data for 2010–2012, mean BLLs among individuals aged ≥10 y were 2.09 μg/dL overall, and 2.44 μg/dL and 1.78 μg/dL for men and women, respectively (KCDC 2012). In 2015, the U.S. National Institute for Occupational Safety and Health established 5 μg/dL as the reference level for BLL in adults and revised the definition of elevated BLL from ≥10 μg/dL (established in 2009) to ≥5 μg/dL (CDC 2018).

In South Korea, mortality due to heart disease increased from 45 per 100,000 in 2009 to 62.4 per 100,000 in 2018, making heart disease the second leading cause of death (KOSIS 2019). The number of patients treated for heart disease in South Korea increased from 1.123 million in 2011 to 1.528 million in 2018, an average annual increase of 4.5%, whereas medical expenses increased by 9.6% per year, from $1,131.5 million in 2011 to $2,151.3 million in 2018 (HIRA 2019). With an aging global population, the global burden of heart disease is expected to increase as well (Joseph et al. 2017).

MSCAS was associated with BLL in the present study population, though BLL was lower than the recommended standard of 5 μg/dL in 94.3% of the participants (2,068/2,193), and only two had BLLs >10 μg/dL. In a prospective cohort of U.S. men, the risk of ischemic heart disease was 1.73 times higher (95% CI: 1.05, 2.87) in men with a BLL of ≥5 μg/dL vs. men with a BLL of <5 μg/dL (Jain et al. 2007). Mortality was higher among U.S. residents with BLLs of 10–19 and 20–29 μg/dL, respectively, compared with <10 μg/dL, based on NHANES BLL data from 1976–1980 and mortality follow-up through 1992 (Lustberg and Silbergeld 2002). A subsequent NHANES study based on BLL data from 1988–1994, with mortality follow-up through 2000, also reported higher mortality with increasing BLLs, though BLL categories were reduced to 5–9 μg/dL and ≥10 μg/dL compared with <5 μg/dL, consistent with the reductions seen in BLLs over time (Schober et al. 2006). The British Regional Heart Study and two other small cohort studies reported positive but nonsignificant correlations between the incidence of coronary artery disease or stroke and BLL (Kromhout 1988; Møller and Kristensen 1992; Pocock et al. 1988). A recent study reported an association between BLL and atherosclerotic plaque in the carotid artery (Harari et al. 2019). Furthermore, BLL has been associated with increased all-cause and cardiovascular mortality, even at low BLLs (Menke et al. 2006; Schober et al. 2006).

Lead exposure is a risk factor for hypertension. Previous studies suggest that lead exposure contributes to the development of ischemic heart disease by increasing blood pressure (Khot et al. 2003; Harlan et al. 1985; MacMahon et al. 1990; Tibblin et al. 1975; Wojtczak-Jaroszowa and Kubow 1989). It has also been proposed that lead exposure might contribute to cardiovascular disease by increasing the risk of atherosclerosis through mechanisms related to cytochrome P-450 inhibition and subsequent lipid deposition; by inhibiting the free radical scavenging enzyme superoxide dismutase, resulting in increased serum lipid peroxide levels; or by interfering with lipid metabolism and increasing serum cholesterol levels (Wojtczak-Jaroszowa and Kubow 1989).

We used stratified models to estimate associations separately for men and women, but estimates for women were based on only 732 participants and 50 MSCAS cases (vs. 1,461 participants and 200 MSCAS cases in men). Although the OR for women [Model 3 OR = 1.10 (95% CI: 0.86, 1.41)] was closer to the null than the OR for men [OR = 1.14 (95% CI: 1.01, 1.28)], the present study lacked sufficient power to assess differences between men and women. Studies involving a larger number of women should be conducted in the future. On average, women also had lower BLLs than men, and it is possible that differences between men and women might partly reflect weaker associations between BLLs and MSCAS at lower levels of exposure. Future studies should use appropriate models to

Table 3. Odds ratios for moderate-to-severe coronary artery stenosis (≥25% stenosis) in association with a 1-μg/dL increase in blood lead level.

Variables	Total (n)	Cases [n (%)][a]	Model	Odds ratio	95% CI	p-Value
All participants	2,193	250 (11.4)	Unadjusted	1.22	1.11–1.34	<0.001
			Model 1[b]	1.16	1.05–1.29	0.004
			Model 2[c]	1.13	1.02–1.26	0.020
			Model 3[d]	1.14	1.02–1.26	0.017
Men	1,461	200 (13.7)	Unadjusted	1.17	1.05–1.30	0.006
			Model 1[b]	1.18	1.05–1.32	0.005
			Model 2[c]	1.13	1.01–1.27	0.034
			Model 3[d]	1.14	1.01–1.28	0.033
Women	732	50 (6.8)	Unadjusted	1.09	0.85–1.40	0.502
			Model 1[b]	1.09	0.86–1.39	0.477
			Model 2[c]	1.10	0.85–1.43	0.459
			Model 3[d]	1.10	0.86–1.41	0.453

Note: Sex was a covariate in models for all participants only. CI, confidence interval.
[a]Moderate-to-severe coronary artery narrowing (≥25% stenosis) cases.
[b]Model 1: adjusted for age and sex.
[c]Model 2: adjusted for age, sex, body mass index, regular exercise, smoking, and alcohol drinking.
[d]Model 3: adjusted for age, sex, hypertension, diabetes mellitus, dyslipidemia, body mass index, regular exercise, smoking, and alcohol drinking.

examine the shape of the exposure–outcome relation for BLL and CAS in detail.

There are some limitations of this study. First, the study population comprised participants who visited a university hospital for a general health examination that cost individual participants (or their employers) more than 900 thousand KRW (approximately 830 USD). In addition, participants were limited to those who elected to have both coronary angiography and BLL measurements in the absence of specific symptoms or clinical indications, and CAS screening was limited to participants without contraindications. Therefore, the prevalence of cardiovascular disease and the distribution of BLLs in the study population were likely to differ from the general population. Second, CAS was classified according to the highest degree of stenosis, regardless of the specific coronary arteries or number of vessels involved. In addition, the study was cross-sectional, with prevalent CAS and BLLs assessed at the time of the examination. If possible, future studies should include a longitudinal assessment of the incidence of new stenosis in the general population, with classification according to the location, as well as the degree of stenosis. Last, the small sample size was a limitation that may have affected the results, particularly for subgroup analyses (i.e., 732 women with 50 cases).

The major strength of this study was that CAS was assessed using 128-slice coronary CT angiography in an asymptomatic population. Multislice CT provides high accuracy for noninvasive detection of suspected obstructive coronary artery disease. Compared with invasive coronary angiography for detection of significant lesions (>50% stenosis) in 103 patients (mean age: 61.5 ± 9.7 y), segment-based sensitivity, specificity, and positive and negative predictive values of the 16-slice CT were 95%, 98%, 87%, and 99%, respectively (Hoffmann et al. 2005). In other studies of patients, the sensitivity, specificity, and positive and negative predictive values of the 16- to 64-slice CT were 82–95%, 95–98%, 87–93%, and 93–99%, respectively (Kuettner et al. 2005; Leschka et al. 2005; Mollet et al. 2005; Raff et al. 2005). In a study of 168 high-risk asymptomatic patients (≥1 major risk factor: hypertension, diabetes, hypercholesterolemia, family history, or smoking), the sensitivity, specificity, and positive and negative predictive values of the 16-slice CT were 100%, 98%, 95%, and 100%, respectively (Romeo et al. 2007). A significant association between BLLs and CAS was found through multislice imaging study in this study. This manuscript could be used as valuable data on the association of lead to cardiovascular disease. Another strength of this study was that as a routine part of the health examination, and to ensure that the use of contrast media was not contraindicated, each participant was interviewed by a physician using a structured questionnaire that was consistent throughout the study period (2011–2018).

In conclusion, BLL was associated with MSCAS in an asymptomatic population, 94% of whom had BLLs below the recommended standard of 5 μg/dL. To prevent and reduce the global burden of cardiovascular diseases, our results suggest that BLLs should be maintained as low as possible.

Acknowledgments

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